REMARKS

Applicant respectfully requests entry of the Amendment and reconsideration of the claims. Claims 2, 3, 9, 12-15, 17-19, 22-33 and 36 are pending. Please cancel claims 5-6, 8, 10, 21, and 43-45 without prejudice or disclaimer. Applicant reserves the right to pursue the cancelled subject matter in one or more continuation applications.

Applicant has amended claims 2, 9, 12, 14, 17-19, and 22-24. Applicant has amended independent method claims 2 and 17-19 to recite "wherein the acetylcholine esterase antagonist is targeted to the liver." Claims 9 and 14 have been amended to include "a pharmaceutically acceptable liver-targeting substance" in the composition and kit, respectively. These amendments are supported throughout the specification, including at page 10, lines 23-31. Applicant has amended claim 12 to delete "at least one of", to establish the abbreviation SIN-1, and to correct an obvious typographical error. Applicant has also amended claims 22-24 to correct the dependency.

Applicants respectfully request reconsideration and withdrawal of the claim objection and pending rejections under obviousness-type double patenting and 35 U.S.C. § 103(a).

Claims Objections

The Examiner objects to claim 12. The Examiner stated that at line 2 after "at least one of" the wording insulin, insulin analog and sulfonylurea should be omitted because page 11 of the specification recites all the compounds described as "insulin, insulin analog and sulfonylurea agents". The Examiner further objected to claim 12 on the basis that the abbreviation SIN-1 should be spelled out when first used and the abbreviation in parenthesis.

Claim 12 has been amended as required by the Examiner to delete "at least one of" and to spell out the abbreviation SIN-1 in full.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejects claims 2, 5, 9-10, 12, 14-15, 17-19, 21, 25-29, 31-32, and 43-45 under 35 U.S.C. § 103(a) as allegedly obvious over Thiele et al. (*Munch. Med. Wochenschr.*, 1957), in view of American Diabetes Association 1998 as evident by drugdelivery.ca and http://syndromex.stanford.edu/InsulinResistance.htm. Claims 14 and 15 are further rejected in view of the aforementioned art and U.S. Patent No. 6,194,454 (Dow). Applicants respectfully traverse these rejections.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. __ (2007). A dependent claim is not obvious if the claim from which it depends is not obvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Applicant respectfully asserts that the Examiner does not make a *prima facie* case of obviousness because all the limitations of the present claims are not taught by the combination of references cited in the Office Action.

Independent method claims 2, 17, 18, and 19 have been amended to include the limitation that the acetylcholine esterase antagonist is targeted to the liver. Independent claims 9 and 14 have been amended to include a pharmaceutically acceptable liver-targeting substance in the composition and kit, respectively. These amendments incorporate the limitation from dependent claims 10 and 21 into all of the independent claims. Now all of the dependent claims require these limitations as well. Support for these amendments can be found at page 10, lines 23-31, and is reproduced below:

> In one embodiment, the acetylcholine esterase antagonist is preferentially targeted to the liver. Targeting of the antagonist to the liver can be accomplished through the use of any pharmaceutically acceptable liver-targeting substance. For example, it can be bound to albumin or bile salts for preferential delivery to liver.

> Alternatively, the antagonist may be incorporated into or encapsulated within liposomes which are preferentially targeted to the liver. In one embodiment, the antagonist is administered in a precursor form, and the precursor is selected to be metabolised to the active form by enzymes preferentially found in the liver.

Applicants respectfully assert that the combination of cited art does not disclose or suggest the limitation of "acetylcholine esterase antagonist is targeted to the liver" or a "pharmaceutically acceptable liver-targeting substance."

The Examiner stated that "[t]he reference teaches neoeserin is a vagotonic functional alteration, (i.e., relating to as defined) therefore targets the liver as required by instant claims 10 and 21" (Office Action at page 4). The limitations required by claims 10 and 21, now incorporated into the independent claims, require targeting the acetylcholine esterase antagonist to the liver. Applicants respectfully disagree that Thiele et al. teaches targeting to the liver. The full quote from Thiele et al. is the following:

> The decisive genetic mechanism of the effect of neoeserin, i.e. its capacity for lowering the sugar level in urine, is probably based on a vagotonic functional alteration of the glycogen storing tissue (muscles and liver), with improved action of the glycogen-storing effect of the (endogenic and exogenic) insulin.

Thus, neoeserin is affecting vagal nerve innervation of the liver (The term "vagotonic" refers to a relationship with the vagus nerve. *See*, page 1902 of Stedman's Medical Dictionary, filed in accompanying IDS). The neoeserin as described by Thiele et al. is affecting the vagus nerve at some position in the body, which then affects the liver. Targeting to the liver (as described in the specification at page 10, lines 23-31) provides a mechanism for an acetylcholine esterase antagonist to be delivered to the liver. Thiele et al. do not describe ***targeting*** neoeserin for delivery to the liver. Thiele et al. is suggesting that neoeserin is affecting the vagus nerve and do not suggest neoeserin activity in the liver.

Additionally, the "vagotonic effect" described by Thiele et al. refers to administered neoeserin exerting an effect throughout all parts of the body which are innervated with the vagus nerve. There is no teaching or suggestion in Thiele et al. that

the orally administered neoeserin is preferentially targeted to the liver as opposed to any other organ innervated by the vagus nerve.

Furthermore, there is no teaching or suggestion in Thiele et al. that targeted administration of neoeserin would be useful for treating insulin resistance or for increasing skeletal muscle glucose uptake in patient suffering from suboptimal hepatic regulation of blood glucose levels. The present inventors were the first to determine the relationship between decreased hepatic acetylcholine levels and insulin resistance. Accordingly, the person skilled in the art having regard to the cited prior art would not have any reason or motivation to treat insulin resistance or to increase skeletal muscle glucose uptake by preferentially targeting an acetylcholine esterase antagonist to the liver.

In regards to the rejection of claims 14 and 15 further in view of the '454 patent, Dow does not remedy the aforementioned deficiencies. Dow does not disclose targeting an acetylcholine esterase antagonist to the liver or any pharmaceutically acceptable liver-targeting substances.

Applicants respectfully assert that the cited prior art--Thiele et al. (*Munch. Med. Wochenschr.*, 1957), drugdelivery.ca, http://syndromex.stanford.edu/InsulinResistance.htm, and U.S. Patent No. 6,194,454—do not teach or suggest targeting an acetylcholine esterase antagonist to the liver or any pharmaceutically acceptable liver-targeting substances. Thereby, the cited art does not teach or suggest all of the claim limitations of the instant independent claims. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

Obviousness-type Double Patenting Rejection

The Examiner provisionally rejects claims 2-3, 5-6, 8-10, 12-15, 17-19, 21-33, 36, and 43-45 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-7, 9, 11, 15, 24, and 32-46 of U.S. Application No. 11/597,032.

Applicant acknowledges the Examiner's rejection for double patenting. Upon indication of allowance, Applicants will file a terminal disclaimer if appropriate.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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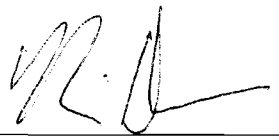

Date: April 29, 2008

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